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Dated 21 July 2006

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28 OCT 2002
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1/77

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P01/7700 0.00-0225041.3

Request for grant of a patent

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Cardiff Road
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1. Your reference — P.86888 GCW

2. Patent application number
(The Patent Office will fill in this part) — 28 OCT 2002 — 0225041.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Ionix Pharmaceuticals Ltd
185 Cambridge Science Park
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083048 91001
Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

SECTION 30 (1977 ACT) APPLICATION FILED 17/3/03

4. Title of the invention — PHARMACEUTICAL FORMULATION

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

J.A. KEMP & CO.

14 South Square
Gray's Inn
London
WC1R 5JJ

Patents ADP number *(if you know it)* 00 0000 26001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

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Continuation sheets of this form	-
Description	10
Claim(s)	2
Abstract	1
Drawing(s)	-

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Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature J.A. KEMP & CO. Date 28 October 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

WOODS, Geoffrey Corlett
020 7405 3292

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GB 0225041.3

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

IONIX PHARMACEUTICALS LTD,
185 Cambridge Science Park,
Milton Road,
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Incorporated in the United Kingdom,

[ADP No. 08304891001]

and

WEST PHARMACEUTICAL SERVICES DRUG DELIVERY
& CLINICAL RESEARCH CENTRE LIMITED,
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Incorporated in the United Kingdom,

[ADP No. 07712573002]

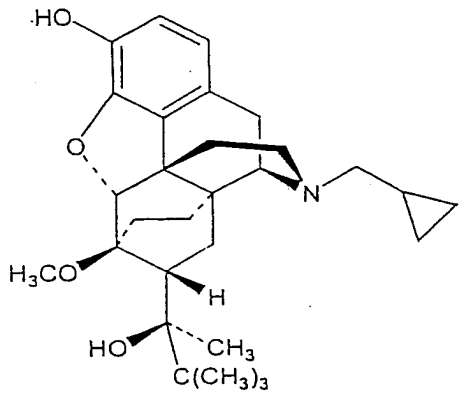
PHARMACEUTICAL FORMULATION

The invention relates to pharmaceutical formulations of buprenorphine and physiologically acceptable salts and esters thereof.

The term opioid (or opiate) defines drugs with morphine-like properties. Opioids can be sub-classified on the basis of their receptor specificity. *Mu*-agonist opioids provide intense analgesia. These opioids can be long-acting (e.g. methadone) or short-acting (e.g. remifentanil).

Mixed agonist/antagonist opioids (e.g. butorphanol and buprenorphine) are partial agonists (the former at *mu* and kappa receptors and the latter at the *mu* receptor) and can produce good quality analgesia. They produce less respiratory depression and constipation than high efficacy *mu* agonists.

Buprenorphine (CAS RN 52485-79-7; [5α,7α(*S*)-17-(Cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol) has the formula:



The hydrochloride is also active (CAS RN 53152-21-9).

Buprenorphine is a highly lipophilic derivative of thebaine. It is a partial *mu* agonist and mediates analgesia at the *mu* opioid receptor. Buprenorphine produces a similar maximum analgesic effect to full *mu* agonists such as morphine in animal models of pain and, although it may have a ceiling effect in certain pain types in man, it has been shown to produce good quality analgesia of similar efficacy to

morphine in most clinical situations including severe pain. An unusual property of buprenorphine observed in *in vitro* studies is its very slow rate of dissociation from its receptor.

As a class, opioids are associated with a number of undesirable side-effects, including respiratory depression, nausea, vomitting, dizziness, mental clouding, dysphoria, pruritus, constipation, increased biliary tract pressure, urinary retention and hypotension. The development of tolerance and the risk of chemical dependence and abuse are further problems. Buprenorphine, however, is unusual in exhibiting a low maximum effect for respiratory depression and also a bell-shaped dose response curve where the effect first increases with larger doses, reaches a ceiling and then diminishes as the dosage is further increased, which makes it a safer drug then morphine, where respiratory depression will ultimately lead to death. Buprenorphine has also been shown to have a lower incidence of other side-effects like constipation in man, and it has a lower abuse potential than full *mu* agonists.

Buprenorphine has previously been administered via the intravenous, intramuscular and sublingual routes to human subjects. There are limited reports of nasal administration. Eriksen *et al*, J. Pharm. Pharmacol. 41, 803-805, 1989 report administration to human volunteers of a nasal spray. The spray consisted of 2mg/ml of buprenorphine hydrochloride dissolved in 5% dextrose and the pH of the solution was adjusted to pH 5.

An improved buprenorphine formulation for nasal administration has now been devised. Rapid uptake of the buprenorphine across the nasal mucosa into the plasma can be achieved, which results in fast onset of analgesia. Further, the residence time of the buprenorphine in the nasal cavity is increased, which results in prolonged analgesia. An improved profile of absorption of buprenorphine into the systemic circulation can thus be achieved by use of the formulation.

Accordingly, the present invention provides an aqueous solution suitable for intranasal administration, which comprises:

(a) from 0.1 to 10 mg/ml of buprenorphine or a physiologically

acceptable salt or ester thereof,

(b) from 0.1 to 20 mg/ml of a chitosan, and

(c) from 0.1 to 15 mg/ml of hydroxypropylmethylcellulose (HPMC);

which solution has a pH of from 3 to 4.8.

The invention further provides a process for the preparation of such an aqueous solution, which comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof, a chitosan and HPMC in water to provide a solution comprising from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof, from 0.1 to 20 mg/ml of chitosan and from 0.1 to 15 mg/ml of HPMC; and adjusting the pH of the solution to a value from 3 to 4.8 as desired.

The invention also provides:

- a nasal delivery device loaded with a solution of the invention;
- use of a solution of the invention for the manufacture of a nasal delivery device for use in inducing analgesia; and
- a method of inducing analgesia in a patient in need thereof, which method comprises intranasally administering a solution of the invention to the patient.

The pharmaceutical solution of the invention consists essentially of 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof, from 0.1 to 20 mg/ml of a chitosan, from 0.1 to 15 mg/ml of HPMC, and water. The buprenorphine salt may be an acid addition salt or a salt with a base. Suitable acid addition salts include the hydrochloride, sulphate, methane sulphonate, stearate, tartrate and lactate salts. The hydrochloride salt is preferred.

The concentration of buprenorphine or buprenorphine salt or ester is from 0.1 to 10 mg/ml, for example from 0.5 to 8 mg/ml. Preferred concentrations are 1 to 6 mg/ml, for example 1 mg/ml or 4 mg/ml, calculated as buprenorphine. The solution of the invention is typically delivered as a nasal spray. A 100 µl squirt of a solution containing 1 to 4 mg/ml of buprenorphine or a buprenorphine salt or ester, calculated as buprenorphine, thus results in a clinical dose of 100 to 400 µg of the buprenorphine or buprenorphine salt or ester, calculated as buprenorphine. Two such

squirts may be given per nostril per administration time to deliver a dose of up to 4 x 400 μg, i.e. up to 1600 μg, of buprenorphine or the buprenorphine salt or ester, calculated as buprenorphine.

A chitosan is present in the solution of the invention. Chitosan is a bioadhesive cationic biopolymer comprising glucosamine and N-acetyl glucosamine. It is prepared by the deacetylation of chitin. In accordance with the present invention, the degree of deacetylation, which represents the proportion of N-acetyl groups which have been removed through deacetylation, should be greater than 40%, preferably greater than 60% and most preferably greater than 70%. The chitosan should preferably have a molecular weight in the range from 10,000 to 1,000,000 Da, more preferably in the range 15,000 to 750,000 Da and most preferably in the range from 20,000 to 500,000 Da.

The chitosan may thus be a deacetylated chitin. It may be a physiologically acceptable salt of a deacatylated chitin. Suitable physiologically acceptable salts include salts with a pharmaceutically acceptable mineral or organic acid such as the hydrochloride, glutamate or lactate salt. A particularly suitable salt is chitosan glutmate, which is available as Protasan (trade mark) UPG213 from Pronova, Norway.

The chitosan may be a derivative of a deacetylated chitin. Suitable derivatives include without limitation ester, ether or other derivatives formed by bonding of acyl and/or alkyl groups with hydroxy groups, but not the amino groups, of a deacetylated chitin. Examples are O-(C_1-C_6 alkyl) ethers of deacetylated chitin and O-acyl esters of deacetylated chitin. Derivatives include too modified forms of a deacetylated chitin for example a deacetylated chitin conjugated to polyethylene glycol.

The aqueous solution of chitosan may be prepared by dissolving chitosan base in a pharmaceutically acceptable mineral or organic acid as hydrochloric, lactic or glutamic acid or by dissolving a pharmaceutically acceptable chitosan salt (for example glutamate or hydrochloride) in water.

The solutions of the invention contain from 0.1 to 20 mg/ml of a chitosan, for example from 0.5 to 20 mg/ml. Preferably the solution contains from 1 to 15 mg/ml, more preferably from 2 to 10 mg/ml, of chitosan. A chitosan concentration of 5 mg/ml is particularly suitable.

Any suitable hydroxypropylmethylcellulose (HPMC) may be employed. Several grades of HPMC are available. For example, Dow Chemical Company produces a range of HPMC polymers under the trade mark Methocel. The grade and concentration of HPMC is chosen such that the solution of the invention preferably has a viscosity, at 25°C as measured by a cone and plate viscometer (e.g. Brookfield), in the range from 1 to 200 cps, more preferably from 3 to 150 cps and most preferably from 5 to 100 cps.

Producing a solution having a particular viscosity is within the capability of one skilled in the at and can be achieved, for example, by using a high concentration of a low viscosity HPMC or a low concentration of a high viscosity HPMC. The HPMC used in the solution of the invention is preferably one having an apparent viscosity (measured as a 2% solution in water at 20°C) in the range from 3000 to 6000 cps. The concentration of the HPMC having a viscosity of from 3000 to 6000 cps is in the range from 0.1 to 15 mg/ml, preferably from 0.5 to 10 mg/ml and preferably from 1 to 5 mg/ml.

Any suitable preservative may be present in the solution, in particular a preservative that prevents microbial spoilage of the solution. The preservative must be compatible with the other components of the solution. The preservative may be any pharmaceutically acceptable preservative, for example a quaternary ammonium compound such as benzalkonium chloride.

A solution of the invention has a pH of from 3 to 4.8. Any pH within this range may be employed provided the buprenorphine or buprenorphine salt or ester remains dissolved in the solution. The pH may be from 3.2 to 4.2, for example from 3.2 to 3.8. A suitable pH is from 3.2 to 3.6 such as from 3.3. to 3.5. The pH may be adjusted to an appropriate value by addition of a physiologically acceptable acid

and/or physiologically acceptable buffer. The pH may thus be adjusted solely by means of a physiologically acceptable mineral acid or solely by means of a physiologically acceptable organic acid. The use of hydrochloric acid is preferred.

Solutions of the invention may include a tonicity adjustment agent such as a sugar, for example dextrose, or a polyhdryic alcohol, for example mannitol. A solution may be hypertonic, substantially isotonic or hypotonic. The osmolality of a solution may be from 0.1 to 0.8 osmol/kg such as from 0.2 to 0.6 osmol/kg or from 0.25 to 0.4 osmol/kg. A substantially isotonic solution can have an osmolality of from 0.28 to 0.35 osmol/kg. An exactly isotonic solution is 0.29 osmol/kg. A suitable osmolality range is from 0.32 to 0.36 osmol/kg. A sufficient amount of a tonicity adjustment agent such as dextrose or mannitol may therefore be present to achieve such osmolalities. Preferably a solution contains 50 mg/ml dextrose or mannitol.

The solution of the invention may also contain other ingredients such as an antioxidant, chelating agent or other agent generally used in pharmaceutical liquid preparations. The solution can be a sterile solution.

A solution of the invention is prepared by dissolving buprenorphine or a physiologically acceptable salt or ester thereof, a chitosan and HPMC in water, typically Water for Injections. The amount of the buprenorphine or salt or ester thereof is selected so that from 0.1 to 10 mg/ml of buprenorphine or the buprenorphine salt or ester is dissolved in the solution. The required concentrations of the chitosan and of HPMC are provided too. A preservative can be dissolved in the solution. The pH of the solution can be adjusted to from 3 to 4.8 as required. Preferably the pH is adjusted by means of hydrochloric acid.

Other components can be provided in solution at any convenient stage. For example, dextrose or mannitol may be dissolved in the water in which the buprenorphine or buprenorphine salt or ester is being dissolved. A sterile solution can be obtained either by using sterile starting materials and operating under sterile conditions and/or by passing the final solution through a sterilising filter. A

pyrogen-free solution can thus be provided. The solution can then be introduced into a nasal delivery device, typically a sterile such device.

The solution of the invention is administered intranasally to a patient in need of analgesia. Rapid onset of analgesia and prolonged analgesia can thus be obtained. An effective amount of buprenorphine or a salt or ester thereof is delivered to a patient. A unit dose can be delivered to one nostril. Alternatively, half of a dose or two doses can be delivered to each nostril each administration time. The dose will depend upon a number of factors including the age and sex of the patient, the nature and extent of the pain to be treated and the period of treatment. A suitable dose of buprenorphine or a buprenorphine salt or ester is from 0.02 to 1.2 mg, such as from 50 to 600 μg or from 100 to 400 μg, calculated as buprenorphine.

Multiple doses of a solution according to the invention may be employed. For example, the rapid onset analgesia produced by the solution of the invention may permit self-titration of analgesic by the patient. The analgesic effect of an initial dose can be quickly and reliably gauged by the patient and, if insufficient, can be immediately supplemented by further dose(s) (often alternating between each nostril) until the required level of analgesia is attained. Multiple dosing may also be used in order to extend pain relief. For example, from 2 to 4 doses per day may be indicated.

The solution of the invention may be used to treat an existing pain condition or to prevent a pain condition from occurring. An existing pain may be alleviated. Solutions of the invention can be used to treat or manage chronic or acute pain, for example the management of post-operative pain (e.g. abdominal surgery, back surgery, caesarean section, hip replacement or knee replacement).

Other medical uses include: pre-operative intranasal administration of the solution of the invention; therapy or prophylaxis adjunctive to anesthesia; post-operative analgesia; the management of trauma pain; the management of cancer pain; the management of endometriosis; the management of inflammatory pain; the management of arthritis pain (including pain associated with rheumatoid arthritis and

osteoarthritis); the management of back pain; the management of myocardial pain (for example ischaemic or infarction pain); the management of dental pain; the management of neuropathic pain (e.g. diabetic neuropathy, post-herpetic neuralgia or trigeminal neuralgia); the management of colic (e.g. renal colic or gallstones), headache, migraine, fibromyalgia or dysmenorrhoea; the management of breakthrough pain associated with malignant and non-malignant disease; and the management of acute procedural pain (e.g. bone marrow aspiration or lumber puncture).

The solutions according to the invention may be administered to the nasal cavity in forms including drops or sprays. The preferred method of administration is using a spray device. Spray devices can be single (unit) dose or multiple dose systems, for example comprising a bottle, pump and actuator. Suitable spray devices are available from various commercial sources including Pfeiffer, Valois, Bespak and Becton-Dickinson.

As already mentioned, rapid onset of analgesia and prolonged analgesia can be achieved by means of the invention. The analgesic delivery profile that can be attained may avoid the relatively high C_{max} values associated with intravenous administration and so lead to an improved therapeutic index. The peak plasma concentration of an analgesic that is attained after administration is defined as C_{max}. The invention can permit reduction or elimination of some or all of the side effects associated with the analgesic.

In preferred embodiments, the delivery agent is adapted to deliver the analgesic component such that $C_{max} = C_{opt}$. The term C_{opt} is used in relation to analgesic drugs which exhibit a dose-response curve to analgesia which is displaced to the left with respect to the dose-response curve for side-effects. The term defines a therapeutic plasma concentration or range thereof which produces acceptable pain relief or pain amelioration but which does not produce side-effects or produces side effects which are less than those associated with higher plasma concentrations.

Preferably, the solution of the invention enables the buprenorphine or salt or

ester thereof to be delivered such that C_{ther} is attained within 30 minutes (for example within 0.5 to 20 minutes such as 0.5 to 15 minutes) after introduction into the nasal cavity. The term C_{ther} defines a therapeutic plasma concentration or range thereof. Thus, the term is used herein to define a blood plasma concentration (or range of plasma concentrations) of the buprenorphine or salt or ester thereof that produces pain relief or pain amelioration.

The T_{maint} is typically from 6 to 24 hours. The term T_{maint} defines the duration of maintenance of C_{ther} after administration of the analgesic. For example, the T_{maint} can be from 7 to 12 hours, from 8 to 12 hours, from 9 to 12 hours, from 10 to 12 hours or from 11 to 12 hours.

The following Examples illustrate the invention.

Example 1: Nasal solution containing buprenorphine (4 mg/ml), chitosan and HPMC

0.75 g of HPMC (Methocel (trade mark) E4M, Colorcon, UK) was dispersed into approximately 125 ml of pre-heated (70-80°C) water for injection (WFI) (Baxter, UK). The HPMC dispersion was stirred in an ice bath until a clear solution had formed. 1.25 g of chitosan glutmate (Protosan (trade mark) UPG213, Pronova, Norway) was dissolved in the HPMC solution. 75 mg of 50% w/w benzalkonium chloride solution (Albright and Wilson, UK) was dispersed in 10 ml of WFI and transferred with an additional 40 ml of WFI to a 250 ml volumetric flask. 1075 mg of buprenorphine hydrochloride (MacFarlan Smith, UK) and 12.5 g of dextrose (Roquette, UK) were transferred into the volumentric flask. The chitosan/HPMC solution and an additional 40 ml of WFI were added to the flask. The solution was adjusted to pH 3.4 using 1M hydrochloric acid solution (BDH, UK) and the flask contents adjusted to 250 ml using WFI.

The final product was a clear colourless solution containing a 4.3 mg/ml buprenophine hydrochloride (corresponding to 4 mg/ml buprenorphine), 5 mg/ml chitosan glutmate, 3 mg/ml HPMC, 50 mg/ml dextorse and 0.15 mg/ml benzalkonium chloride. The osmolity of the final solution was 0.34 Osmol/kg and

the viscosity, as measured using a Brookfield CP70 cone and plate viscometer was 84.7 cps at 2.5 rpm and 25°C.

Single dose nasal spray devices (Pfeiffer, Germany) were filled with the solution. Each device was filled with 123 µl of liquid. Acutation of the device delivered a dose of 100 µl of liquid containing 400 µg of buprenorphine, 0.5 mg of chitosan and 0.3 mg of HPMC. Hence, a dose of 400 µg buprenorphine is provided by a single spray into one nostril. A dose of 800 µg is provided by a single spray into each nostril.

Example 2: Nasal solution containing buprenorphine (1 mg/ml), chitosan and HPMC

A solution containing HPMC, chitosan glutamate and benzalkonium chloride is prepared according to Example 1. 269 mg if buprenorphine hydrochloride and 12.5 g of mannitol (Sigma, UK) are transferred into the volumetric flask. The chitosan/HPMC solution and an additional 40 ml of WFI are added to the flask. The pH of the solution is adjusted to pH 3.6 using 1M hydrochloric acid solution and the flask contents adjusted to 250 ml using WFI.

The final product is a clear colourless solution containing 1.08 mg/ml buprenorphine hydrochloride (corresponding to 1 mg/ml buprenorphine), 5 mg/ml chitosan glutmate, 3 mg/ml HPMC, 50 mg/ml mannitol and 0.15 mg/ml benzalkonium chloride.

123 µl of the above solution is filled into a single dose nasal spray device (Pfeiffer, Germany). Actuation of the device will deliver a dose of 100 µl of liquid containing 100 µg of buprenorphine, 0.5 mg of chitosan and 0.3 mg of HPMC.

5ml of the solution is filled into a 10 ml glass bottle. A Valois VP7, 100 µl pump and actuator (Valois, France) are attached to the bottle. When primed, the pump will dispense 100 µl of solution containing 100 µg of buprenorphine.

CLAIMS

1. An aqueous solution suitable for intranasal administration, which comprises:

(a) from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof,

(b) from 0.1 to 20 mg/ml of a chitosan, and

(c) from 0.1 to 15 mg/ml of hydroxypropylmethylcellulose;

which solution has a pH of from 3 to 4.8.

2. A solution according to claim 1, wherein the buprenorphine or buprenorphine salt or ester is present in an amount of from 0.5 to 8 mg/ml.

3. A solution according to claim 2, wherein the buprenorphine or buprenorphine salt or ester is present in an amount of from 1 to 6 mg/ml calculated as buprenorphine.

4. A solution according to any one of the preceding claims, which comprises buprenorphine hydrochloride.

5. A solution according to any one of the preceding claims, wherein the chitosan is present in an amount of from 2 to 10 mg/ml.

6. A solution according to any one of the preceding claims, wherein the chitosan is a physiologically acceptable salt of a deacetylated chitin.

7. A solution according to claim 6, wherein the salt is chitosan glutamate.

8. A solution according to any one of the preceding claims, wherein the hydroxypropylmethylcellulose has an apparent viscosity of from 3000 to 6000 cps and is present in an amount of from 0.5 to 10 mg/ml.

9. A solution according to any one of the preceding claims, wherein the pH is from 3.2 to 3.8.

10. A solution according to any one of the preceding claims, wherein the pH has been adjusted by means of hydrochloric acid.

11. A solution according to any one of the preceding claims, which

comprises a preservative.

12. A solution according to claim 11, wherein the preservative is benzalkonium chloride.

13. A solution according to any one of the preceding claims, which has an osmolality of from 0.25 to 0.4 osmol/kg.

14. A solution according to any one of the preceding claims, which contains dextrose as a tonicity adjustment agent.

15. A process for the preparation of an aqueous solution as defined in claim 1, which process comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof, a chitosan and hydroxypropylmethylcellulose in water to provide a solution comprising from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof, from 0.1 to 20 mg/ml of chitosan and from 0.1 to 15 mg/ml of hydroxypropylmethylcellulose; and adjusting the pH of the solution to a value from 3 to 4.8 as desired.

16. A process according to claim 15, wherein the resulting solution is introduced into a nasal delivery device.

17. A nasal delivery device loaded with a solution as claimed in any one of claims 1 to 14.

18. A device according to claim 17, which is a spray device.

19. Use of a solution as defined in any one of claims 1 to 14 for the manufacture of a nasal delivery device for use in inducing analgesia.

20. A method of inducing analgesia in a patient in need thereof, which method comprises intranasally administering an aqueous solution as defined in claim 1 to the patient.

ABSTRACT

PHARMACEUTICAL FORMULATION

An aqueous solution suitable for intranasal administration comprises:

(a) from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof,

(b) from 0.1 to 20 mg/ml of a chitosan, and

(c) from 0.1 to 15 mg/ml of hydroxypropylmethylcellulose;

which solution has a pH of from 3 to 4.8. Such formulations can induce rapid and prolonged analgesia.